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Editorial

Advance

In October the Medical Society held its first Open Meeting of the Session 1941-42. Many students did not attend this meeting and consequently did not see history being made. For history *has* been made.

The Open Meeting was called for the express purpose of discussing what was to be done about the disorder which occurred at the Medical Banquet. It was never a "protest" meeting. The programme was constructive from the outset.

The staff of the Faculty, and the ruling body of the University were incensed, and certainly not without justification. A disorder had occurred, a disorder which was deemed beyond the limits of "good fun." Their duty was clear: a recurrence was to be prevented.

The Medical Society executive could see what was in the air. The senior men had seen it before, over the question of Daffydil Night. They had also seen the results of the Caput's decision. True, prohibiting the show had removed the causes for complaint, but it had left a feeling of injustice in the minds of the students which rankles to this day, it had caused a further cleft between students and professors already too wide, and it had removed from the students one of their privileges, cherished by them as any democracy cherishes its freedom. What, then, was to be done? The only solution the executive could see was that the students discipline themselves. Such disciplinary powers required an amendment

to the constitution of the Medical Society, and such an amendment was passed at the meeting.

Now, the student body has disciplinary powers invested in five of its elected members, in the form of a "Student Caput." This student caput has power to administer such punishment to offending members as it thinks necessary and appropriate, even to the extent of recommending expulsion. Of course, any student receiving punishment has the right to appeal to the higher authorities, should he think he has been treated wrongly.

The immediate effect of this amendment is obvious. The danger of prohibition of future banquets and of several expulsions has been averted. But there are greater, more far reaching considerations. To the best of our knowledge, such power has never before been given to a student body at the University of Toronto, with the full approval of the Faculty. This is an advance in the direction of self-government, to the pristine state of university students. And it is a step taken at a time when there is prospect of self-government being taken away from the whole medical profession.

Most students know, if they read last month's JOURNAL, that there is a movement afoot to have what amounts to State Medicine in Canada.

The medical profession has a high public responsibility. Unfortunately, it has not accepted as a body this full responsibility, nor taken any steps to overcome or circumvent the faults which are to be found in the present system, and as a result such steps are being taken outside the profession. In other words, orders are to be handed down from above, just as happened to the medical students over Daffydil Night, and the chances are that they will be little better received.

What is to be done? At the present moment, very little. It is the desire of this JOURNAL, however, to awaken in the medical students of to-day, who are the doctors of to-morrow, a deeper sense of their public responsibility, that the day may come when they will be able to put forth and stand behind, as a body, a plan which will be acceptable to all parties.

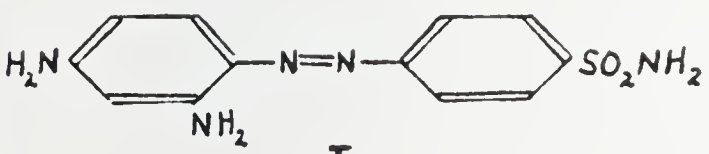
It is to this end that the JOURNAL presents to its readers, in this and other issues, articles on the economics and problems of medicine. It is hoped that they will be read and given thought.

THE METABOLISM OF CHEMOTHERAPEUTIC AGENTS OF THE SULPHONAMIDE GROUP

By LESLIE YOUNG, Ph.D. (Lond.), B.Sc., A.R.C.S., F.I.C.
Associate Professor of Biochemistry,
University of Toronto

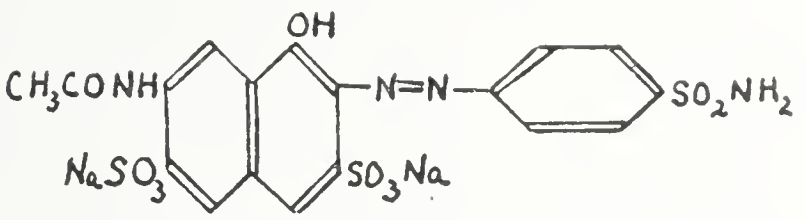
If a chemotherapeutic agent is to be used intelligently, it is desirable that there shall be an understanding of its mode of action with respect to both the host and the invading organism. Chemotherapeutic agents, like other organic compounds, are liable to undergo chemical change when they come in contact with living cells. Such metabolic changes have an important bearing on the action of these agents. In some cases therapeutic activity is a property, not of the administered compound but of a substance derived from it by metabolic action. In other cases the metabolic changes to which the drug is subjected render it therapeutically inactive. Certain toxic reactions may be associated with the metabolic changes which the compound undergoes, whereas some of the metabolic products derived from the drug may be less toxic than the drug itself. From such considerations it follows that a knowledge of the metabolism of a chemotherapeutic agent is essential for an understanding of its action. This is well borne out in the case of the sulphonamide drugs.

The publication in 1935 of Domagk's (1) finding that administration of "Prontosil", an azo dye, 4-sulphonamido-2', 4'-diaminoazobenzene (I), has a curative effect on experimental streptococcal infections in mice was followed rapidly by an appreciation of the value of this agent in the treatment of human infections.



I

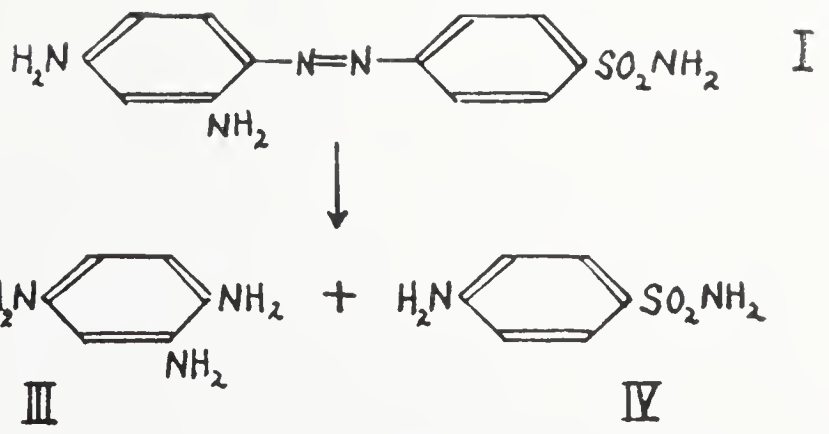
In his original report on "Prontosil" Domagk drew attention to the fact that the compound is without bacteriostatic or bacteriocidal effect in vitro, and that it is effective only in vivo. Subsequent work (2, 3, 4) led to similar findings with respect to an allied compound, the disodium salt of 4'-sulphonamidophenyl-2-azo-1-hydroxy-7'-acetylaminonaphthalene-3, 6-disulphonic acid (II), a substance marketed under the names "Prontosil Soluble" and "Neoprontosil".



II

Attempts to explain the fact that these drugs are active only in vivo led to the formulation of a variety of hypotheses. For example, the possibility was suggested that the defense mechanisms of the host are activated. The suggestion was also advanced that capsule formation is prevented and the streptococci thereby rendered susceptible to phagocytosis (5).

Late in 1935 there appeared a paper by Tréfouël, Tréfouël, Nitti and Bovet (6) which greatly influenced the subsequent course of research on the sulphonamide drugs. These workers stated that in their opinion "Prontosil" is metabolised in the body of the host giving rise to 1, 2, 4-triaminobenzene (III) and p-aminobenzenesulphonamide (IV). This change

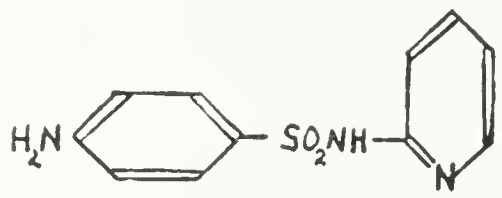


I

III IV

involves the reduction and fission of the "Prontosil" molecule at the azo linkage. The Tréfouëls and their collaborators found that p-aminobenzenesulphonamide

(IV), like "Prontosil" itself, has a curative effect on streptococcal infections in mice. Furthermore, they established that p-aminobenzenesulphonamide shows bacteriostatic activity in vitro (7). While their findings did not prove that the therapeutic activity of "Prontosil" is related entirely to p-aminobenzenesulphonamide derived from it in the body, they nevertheless established the important fact that the presence of azo linkage in a sulphonamide compound is not essential for the therapeutic activity. The widespread study of p-aminobenzenesulphonamide (now commonly known as sulphanilamide) which followed these observations led quickly to an appreciation of the remarkable antibacterial activity of this compound in vivo, and investigations on the therapeutic activity of its derivatives resulted in the discovery of new chemotherapeutic agents. Prominent among these are 2-(p-aminobenzenesulphonamido) pyridine (V), better known as sulphapyridine, M and B 693 or "Dagenan", and 2-(p-aminobenzenesulphonamido) thiazole (VI), a substance known as sulphathiazole, M and B 760, or Ciba 3714.



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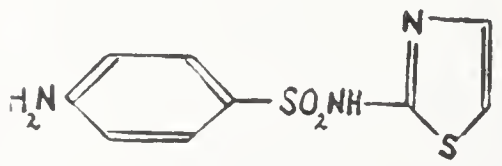
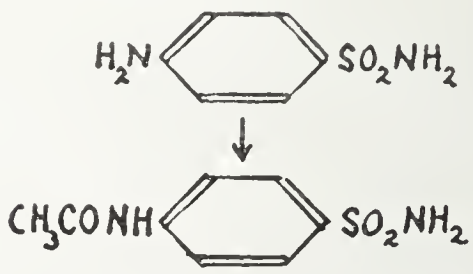


VI

The view that the therapeutic activity of azo dyes such as "Prontosil" and "Neoprontosil" is dependent upon their reduction in the body to sulphanilamide has been opposed by certain workers (8). It has been shown, however, that the therapeutic activity of a dose of sulphanilamide corresponds closely to that of a molar equivalent dose of "Neoprontosil" (9). Furthermore, by isolating sulphanilamide from the urine of patients and experimental animals receiving "Prontosil" or "Neoprontosil", Fuller (3) has established that a breakdown of these drugs does take place in the body.

In man and various other mammals sulphanilamide is excreted partly in the form of its acetyl derivative, p-acetylaminobenzenesulphonamide (VII) (10).



IV

VII

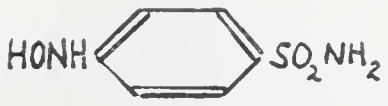
Sulphapyridine (11) and sulphathiazole (12) have also been shown to undergo some degree of acetylation in man. That such a change occurs is not surprising, for it has long been known that foreign carbocyclic compounds with nuclear amino groups are acetylated in the animal body. A notable exception to this is found in the case of the dog. Although the acetylation of an amino group situated in a side chain of an aromatic compound takes place in this animal, this type of reaction does not appear to occur if the amino group is attached directly to an aromatic nucleus. In consequence of this, whereas acetylation of sulphanilamide has been shown to take place in many species, it does not occur in the dog (13).

In assessing the significance of metabolic acetylation on the action of sulphonamide agents there are several factors to be considered. Acetylation of a sulphonamide drug appears to render it therapeutically inactive. The rate of acetylation of the drug and the extent to which this reaction proceeds are therefore factors which serve to limit therapeutic action. Since the proportion of the drug which is acetylated varies widely in different individuals, it seems not unlikely that this accounts, in part at least, for variations in response to sulphonamide therapy.

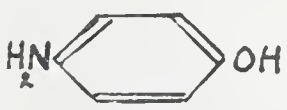
The acetylation of drugs of the sulphonamide group can hardly be regarded as a detoxication mechanism. The acetylation occurs at the expense of a withdrawal of acetyl-precursors from the body, and there is evidence (14, 15) which suggests that this process gives

rise to acute toxic effects. Furthermore, it has been established that acetylsulphanilamide, when administered as such, is more toxic than sulphanilamide (10, 14).

Another effect attendant upon the acetylation of certain sulphonamide drugs in vivo is that it gives rise to products whose solubility is such that they are liable to undergo precipitation in the urinary tract. The formation of renal calculi consisting largely of the acetyl derivative of sulphapyridine has been reported (16). There are also records of cases of haematuria following sulphapyridine therapy which were apparently due to mechanical injury to tissues of the urinary tract by spicules of acetylsulphapyridine. The problem of urolithiasis in sulphonamide therapy has been studied recently by Martin, Rennebaum and Thompson (17). These workers report that they were able to block completely the acetylation of sulphanilamide in rats by the administration of glucuronic acid.

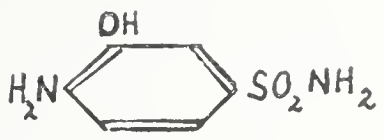


VIII



IX

The chemical changes to which sulphonamide drugs are subjected in the animal body are not limited to the formation of acetyl derivatives. Oxidation of the drugs is known to take place, although uncertainty surrounds the identity of some of the oxidation products. It has been reported (18) that p-hydroxylaminobenzenesulphonamide (VIII) and p-aminophenol (IX) are present in the urine following the administration of sulphanilamide. Recent work (19) throws doubt on such claims on the ground that they are based largely on the results of certain colour reactions which are by no means specific. Various workers are agreed, however, that there is a rise in the ethereal sulphate content of the urine after the ingestion of sulphanilamide, and this would suggest that oxidation of sulphanilamide to a hydroxy derivative takes place in the body. The oxidation of certain aniline derivatives in vivo is known to occur in the ortho or para position with respect to the amino group, and since the ortho position is available in sulphanilamide, it may be that formation of 1-amino-2-hydroxybenzene-4-sulphonamide (X) from sulphanilamide occurs in the body, although neither this substance nor its sulphate has yet been isolated from the urine.

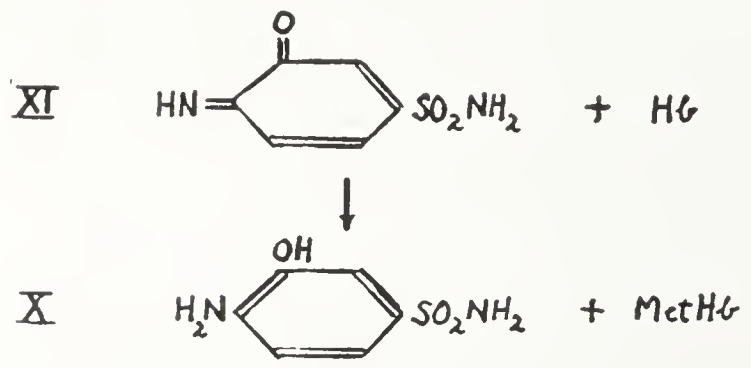


X

A hydroxy derivative of sulphapyridine and its corresponding glucuronide have been isolated from urine obtained after sulphapyridine administration (20).

The characterization of the oxidation products formed from sulphonamide drugs in the body has attracted some attention because of the possible relationship of these substances to certain toxic reactions, such as cyanosis, which occur during sulphonamide therapy. There has been some controversy concerning the nature of the substance responsible for the darkening of the blood. Methaemoglobin has frequently been shown to be present in the blood of patients following sulphanilamide administration (21, 22, 23), and it has been reported that there is a close correlation between the amount of spectrophometrically determined methaemoglobin and the degree of cyanosis (22, 24, 25). There are some workers (26, 27) who suggest, however, that the abnormal colour of the blood may be due to the presence of coloured derivatives of the drug. Porphyrinuria, due mainly to an excretion of coproporphyrin III, has been reported (28, 29) in human clinical cases undergoing sulphanilamide treatment, and this is probably related to abnormal destruction of haemoglobin. Rimington and Hemmings (30) state that in general those agents which exert porphyrinuric action also produce methaemoglobinaemia, and that the same chemical grouping is responsible for both

effects, namely, ". . . an aromatic amino group, unsubstituted and potentially free and preferably situated in such a system that it is capable of undergoing oxidation with the formation of a hydroxylamine derivative or a reversibly oxidizing system such as a p- or o-iminoquinone." Although convincing evidence for the formation in vivo of a hydroxylamine derivative of sulphanilamide has not been forthcoming, it seems possible that 1-amino-2-hydroxybenzene-4-sulphonamide (X) may be formed. Further oxidation of this substance in the body would give rise to an o-iminoquinone (XI). This might be expected to convert haemoglobin to methaemoglobin according to the following reaction:



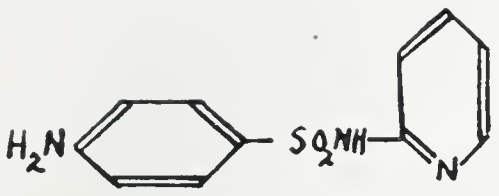
Reoxidation in the tissues of the aminophenol (X) to the iminoquinone (XI) would permit the repetition of the above reaction with the formation of more methaemoglobin. In such a cyclical process one molecule of the iminoquinone could bring about the conversion of many molecules of haemoglobin to methaemoglobin.

While it is known that drugs of the sulphonamide group are subjected to metabolic changes within the animal body, there is, as yet, no direct evidence to show that they undergo chemical change by interaction with bacteria. According to modern views (31) sulphanilamide exerts an antibacterial action by competing for a bacterial enzyme associated with a metabolite necessary for the growth of the organism. Support for this hypothesis can be drawn from the recent finding that p-aminobenzoic acid (XII) counteracts the action of sulphanilamide in vitro (32) and in vivo (33). It is well known that a normal metabolic process can be inhibited by a foreign compound which competes for the enzyme which catalyses that process. It is also known that the most likely substances to

exert such an inhibitory action are those related structurally to the metabolite associated with the enzyme. When the activity of an enzyme is essential for the growth of an organism it is clear that any factor which interferes with the normal function of that enzyme will inhibit growth. If, as seems probable, p-aminobenzoic acid is a metabolite essential for bacterial growth, it becomes possible to interpret the antibacterial action of the chemically related compound sulphanilamide (c.f. IV and XII) in terms of its competing for the enzyme associated with p-aminobenzoic acid in bacterial metabolism. The position has been admirably summarized by Fildes (31) as follows: "Antibacterial substances function by 'interfering' with an essential metabolite and thus inhibit growth. The interference may be (1) by oxidizing a substance which requires to be reduced, (2) by molecular combination forming an inactive product, or (3) by competition for an enzyme associated with the essential metabolite. It is claimed that sulphanilamide acts as in (3), the essential metabolite being p-aminobenzoic acid. Class (3) inhibitions require an inhibitor so closely related in formula to the essential metabolite that it can fit the enzyme, and sufficiently unrelated to be devoid of essential metabolic activity." Fildes goes on to suggest that "research in chemotherapy might reasonably be directed to making such modifications of known essential metabolites as will have these characters."

Investigations made during recent years have led to the identification of a number of compounds which play essential rôles in bacterial metabolism. Among such compounds are nicotinic acid and thiamin (vitamin B_1). This is of particular interest in view of the fact that nicotinic acid

and sulphapyridine have a major chemical group in common, as also have thiamin and sulphathiazole. In the case of nicotinic acid (XIII) and sulphapyridine (V), the pyridyl group is common to both compounds.



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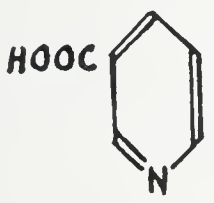
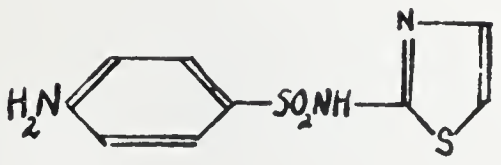


XIII

Thiamin (XIV) and sulphathiazole (VI) both contain a thiazole group.



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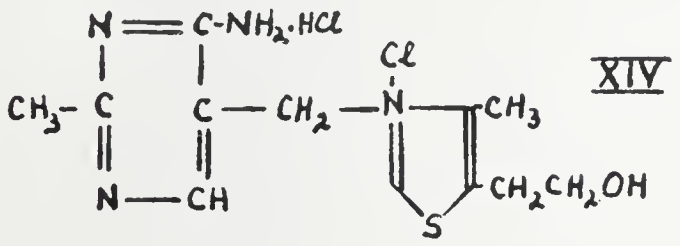

XIV

While it might be argued that these structural similarities are fortuitous, they nevertheless give weight to the possibility that a chemotherapeutic agent, by virtue of its structural relationship to an essential metabolite, may inhibit a bacterial enzyme associated with that metabolite.

Hitherto a lack of fundamental knowledge has impeded the search for new chemotherapeutic agents. This search will be greatly facilitated if further investigation should prove the soundness of the above interpretation of their mode of action.

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HAEMATURIA

By R. F. WARREN, B.Sc., 4T4

Whenever reference is made to blood in the urine, that blood may be present in one or both of two forms. First there may be free red blood cells and red cell clots or secondly there may be free haemoglobin of ruptured cells, in which case the red cell "ghosts" may or may not also be found. Strictly speaking this latter condition should be classed separately as Haemoglobinuria but because of common usage, including that of Peters and Van Slyke, the broader interpretation will be adopted here.

A great many conditions give rise to haematuria. In some the presence of red cells is diagnostic. Nor are the conditions which give rise to it always pathological for as we shall see there are also normal and physiological conditions where blood may be expected or where its presence casts no reflection on the genito-urinary system.

Before proceeding with the discussion of these many conditions it is important to observe the time during micturition when blood first makes its appearance, and also the gross appearance of the urine at time of voiding.

If the blood is diffusely mixed with the urine the suggestion at once is that the lesion is in the kidneys. Here the two fluids diffuse in the pelves and ureters as they are produced synchronously.

When blood appears discrete, suspicions fall on a lower urinary site. If it appears early the urethra or prostate are probably involved whereas if it is seen late the bladder itself should be examined.

Sometimes, as on renal haemorrhage following trauma, blood clots will be passed. These may have settled to the floor of the bladder, but a history of renal colic as they passed down the ureters will cause symptoms of excruciating pain. The patient may seek medical relief for this pain before he is aware of the haematuria.

The quantity of blood varies greatly with the different lesions. Sometimes the presence of blood is obvious from the colour and consistancy it imparts to the urine. At others there is a general smoky colour, while in cases of minute haemorrhages the red cells will only be found on microscopic examination after centrifuging.

SITES OF BLEEDING

Those most commonly met are (1) the kidneys and pelves, (2) the ureters, (3) the bladder, (4) the prostate and the urethra.

1. THE KIDNEYS AND PELVES

A. Toxic conditions causing haematuria

i. *Acute Glomerulonephritis*

In the acute or primary stage of glomerulonephritis the most obvious lesions are in the glomerular tufts. On microscopic examination the surrounding capsular spaces are filled with red blood cells, in the exudate from glomerular capillaries. As the tufts become more cellular, the space occluded and finally filled with hyaline material the cause for haematuria is removed. Accordingly we would not expect to find red cells in the urine of patients with subacute or chronic stages of this disease. Furthermore the tubules in these latter stages are undergoing an ischaemic degeneration. Should blood be found it offers convincing evidence of a continuing inflamatory reaction within the kidney.

In the acute stage, albuminuria and hypertension are frequent accompaniments of haematuria.

ii. *Recurrent acute glomerulonephritis*

This condition is described by some as an acute glomerulonephritis presenting recurrent attacks of albuminuria, haematuria and hypertension, but with few, if any, of these symptoms during the quiescent periods. Sometimes a mild hypertension persists.

iii. *Acute interstitial nephritis*

rarely accompanies scarlet fever and diphtheria. No bacteria are found in the kidneys and the glomeruli and tubules are seldom seriously damaged. The condition may be regarded as transient and toxic. The urine shows slight albuminuria and a few lymphocytes and red blood cells.

B. Bacterial Invasions of the kidneys causing haematuria

i. *Embolic glomerulonephritis*

When mycotic emboli become lodged in glomerular capillaries they have a tendency to pass through a portion of the tuft before being stopped. The proximal parts are therefore supplied with blood whereas necrosis results in the occluded distal portion. Until repair and fibrosis have taken place the capsular space will be found filled with red blood cells, which pass readily into the urine. Because only some of the glomeruli are involved renal insufficiency seldom develops, and the only clinical sign may be the haematuria.

ii. *Focal nephritis*

This condition accompanies tonsillitis and streptococcal sore throat and may cause haematuria within two weeks of the primary infection. Sometimes it follows malaria and typhoid fever with casts in the urine and albuminuria. Bacteria are found in the kidney and in the urine. The glomerular haemorrhage into the capsular spaces is often excessive and Bayliss states that sometimes nephrectomy has to be resorted to when horse serum and other means fail to halt the loss of blood.

iii. *Syphilitic nephritis*

In the later stages of this disease haematuria is observed as a result of the glomerulonephritis which develops. This is a rare condition.

iv. *Tuberculosis of the kidney* (primary or surgical tuberculosis)

The patient is more commonly male than female and usually a young adult. The urine is acid and may contain varying quantities of pus, caseous material and disintegrating mucous membranes, tubercle bacilli are found on centrifuging the urine. Haematuria may be a consistant feature, though a few cases are on record where it has failed to appear. Bleeding takes place in the kidney when small vessels in the renal papillae are destroyed. It may be profuse and when the blood clots in the pelves it produces characteristic exacerbations as well as the dull aching pain. These pains, known as *renal colic*, are similar to those felt on the passage of stones down the ureter.

The identification of the bacteria, and the cystoscopic examination of the ureter producing the blood may aid in diagnosis and treatment. There is a strong tendency for this constant flow of contaminated urine down ureters and into the bladder to set up tuberculous ulcers in the lower urinary tract. These ulcers are common sites of very large haemorrhage into the urine.

C. Conditions of the kidney related to cardiovascular changes

Bleeding of the glomeruli into capsular spaces may result from two general conditions which raise the intracapillary pressure. These are:

i. *Venous congestion*

where a large back pressure is built up as in a failing heart. Together with all the other vessels leading to the right side of the heart the glomerular capillaries are distended, engorged with blood and stasis may result. Thus, in a failing heart it is not uncommon for the patient to find blood in the urine and for similar reasons that he might report blood in the sputum.

ii. *Hypertension*

of the "malignant type" again causes the glomeruli to become engorged and red cells are found in their exudate. This is the Haematuria of Malignant Hypertension.

iii. *Infarction of the kidney*

results in blood in the urine. The breakdown of glomeruli and tubules when their common blood supply is shut off is accompanied by a peripheral zone of congestion. Into this latter there may be a great deal of haemorrhage which accounts for the haematuria.

D. Cysts and Tumours producing haematuria

i. *Congenital cystic kidney*

The outstanding feature of this disorder is the appearance of great numbers of variegated cysts of the kidney. Some of these are filled with clear watery fluid, others are milky and a few are brown or red indicating their blood relationship. When these last make a further communication with the pelvis of the kidney blood appears in the urine. This may be the first indication of the cystic kidney.

ii. *Papilloma of the renal pelvis*

Fortunately a rare condition, this disease is characterized by a villous mass in the cavity of the renal pelvis similar to that met with in the bladder. It occurs in older people with excessive haematuria.

iii. *Angioma of the renal pelvis*

is another rare innocent growth of the renal pelvis causing a painless haematuria.

iv. *Hypernephroma (Grawitz Tumour)*

is the commonest of all renal tumours and accounts for about 75-80%. It is found in adults of middle and advancing years. Haematuria is often the first symptom but unfortunately by no means a symptom of early growth (present in 50%). Bleeding causes pain of two types: (i) a dull aching pain which may be very severe and (ii) a colicky pain due to the passage of clots down the ureter.

E. Hydronephrosis

may be caused by a multitude of conditions. Without entering into a discussion of these here it should be pointed out that the symptoms may frequently be due to the causative agent rather than due to the hydronephrosis itself. Amongst these symptoms haematuria may be very marked as in the impaction or ulceration caused by a stone. Sometimes haematuria is observed for which no satisfactory explanation can be found.

F. Trauma

The lesions which a kidney can suffer without extensive external injuries are remarkable. From bodily blows and buffetings the kidney may be reduced to a pulp and extensive haemorrhage be produced. Large amounts of blood and clot are found in the urine unless the ureter becomes occluded. In cases of rapid haemorrhage the blood commonly clots on the walls of the bladder and may prevent the emptying of that organ.

2. THE BLADDER

The common causes of bleeding are:

i. *Ulcers* associated with tuberculosis of the kidney itself and ulceration caused by calculi. The stonelike aggregations of body salts may be smooth or very spiked depending on their constituents and their manner of production. After violent bodily shakings these cause cystic haemorrhage. Their effects on persons engaged in army tanks and armoured vehicles is left to the imagination.

ii. *Tumours* of the bladder commonly take the form of finely divided fibrils suspended like seaweed in a sea of urine. The fibrils are well supplied with blood vessels. When the bladder is emptied the papillomatous suspensions collapse and the contracting muscles damage and tear them. This occasions profuse bleeding towards the end of the act of micturition.

3. THE PROSTATE AND URETHRA

The commonest causes of haemorrhage in these sites is ulceration due to tuberculous lesions or from impacted impassable stones.

The possibility of damage done accidently or intentionally by the introduction of foreign bodies or a poorly manipulated catheter should be borne in mind. There are many cases on record where perversions of one sort or another have led to the introduction of weird objects. In one case reported in the B.M.J. a small garter snake, in an advanced stage of decomposition, was found to be the cause of a profuse cystic haemorrhage. These cases are rare but may be the solution in obstinate conditions.

4. PHYSIOLOGICAL HAEMATURIA

Under this title is included those conditions where blood is detected in the urine and where no organic lesions are found or where haemolytic changes have taken place in the blood.

i. When there has been active destruction of blood in haemolytic poisons (snake venoms) or through the transfusion of incompatible bloods. The tubules may become occluded unless the urine is alkaline.

ii. It has been recorded by Feigl that blood appears in the urine in the untrained after strenuous physical exercise. He examined the urine of a number of untrained soldiers after a forced march and found haematuria and haematin stained serum in a high percentage of cases.

Broun found an increase of 500% in the reticulocytes without haematuria when the soldiers did similar work but were trained. He found the haematuria reported by Feigl was due to the swelling and leakage of haemoglobin from red cells in the acidosis following excess exercise.

iii. Finally a condition should be made for those cases which defy all other classifications. These are the Essential Haematurias—a convenient but flexible group which dwindles as the pathologist learns more of the causes of haematuria.

5. SCHISTOSOMIASIS

The subject of haematuria cannot be concluded without a brief note on this interesting cause of Egyptian Haematuria. One person in six in Egypt is bedridden with the disease while half the entire population is infected. Haematuria is the common symptom. The disease is very ancient for Ruffer in 1910 discovered the ova of the parasites causing it in mummies of the twentieth dynasty. (1250-1000 B.C.). The inscriptions of many ancient papyri contain prescriptions against it. In Japan a very similar parasite is found which again is a common cause of haematuria. The disease here is known as Katayama Disease.

In 1909 Fujinami, Katsurada, Nakamura and others proved the infection of man with the parasite took place through the skin. Since then the complete life cycle of the weird causative agent has been unfolded, mainly through the work of such men as Leiper, Iturbe, Gonzalez and Lutz.

The little worm varies from 9 to 22 mm. in length. It is grayish white and inhabits the veins of the host, which is always man (the sooty monkey is the only known other host). The worm clings to the intimal surface by strong suckers and the female works upstream as far as the size of the veins will permit. The vessels most commonly selected are the superior and inferior mesenteric and the eggs are laid in the vesical and prostatic plexuses (sometimes the rectal plexus of veins). Here the eggs hatch and work their way out of the body with the faeces and urine. It is at this time that haemorrhage commonly takes place.

Mohammedan religion demands the rigid cleansing of the anal and urethral openings with water after defaecation and urination. In order to comply with this custom the villagers perform their natural duties on the banks of or in the village stream. This enables the voided parasite to seek the second host with ease. A water snail must be found to complete the life cycle and this must be done within 48 hours or the trematode dies. The parasite reinfects man by entering with the drinking water which contains the circariae, or when he bathes in infected streams and canals or by his working in rice fields. Entrance is made through hair follicles and after six weeks young schistosomes are found in the liver.

Finding the portal vein they work slowly upstream where they lay eggs and repeat the cycle in the second host.

Narabayashi found the parasite in the faeces of three out of 22 newborn babies, the parasite being transferred from the mother to the foetus in utero.

CONCLUSION

Some of the commoner causes of Haematuria have been considered from the

standpoint of lesions within and without the urinary tract. The sites of the haemorrhage have been considered separately and the manner of production outlined. Finally a brief note has been made on one of the frequently seen tropical diseases whose commonest symptom is Haematuria.

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The author is indebted to Dr. W. Robinson for reading this paper.

NEUROHUMOURS

By R. G. S. ARTHURS, '43

The manner in which the activity of a nerve fibre brings about a corresponding activity in the effector systems of the body has long been a problem of great interest to many investigators. A direct continuity between each effector cell and a nerve fibre, or its branches, can not be demonstrated, in a great many instances. Evidently, some intermediate factor must be concerned with the transmission of the message from the nerve terminus to the effector cell. Most of the available information indicates that the intermediate factor is a chemical mediator.

Elliot, in 1904, first offered the suggestion that the mediator between the nerve terminal and the effector cell might be a chemical substance. He had observed that the structures, previously innervated by sympathetic fibres, responded in a characteristic fashion to adrenaline, upon degeneration of these fibres. It has since been shown by Cannon and Rosenblueth that the substance or substances released at sympathetic terminals are not identical with adrenaline, although their actions are very similar. These substances have been named "sympathin E and sympathin I".

Sympathin E is liberated in structures *excited* by sympathetic impulses e.g.—cardiac muscle, liver vessels, and smooth muscle of the skin, etc. Sympathin I is liberated in structures *inhibited* by sympathetic impulses, e.g.—intestinal wall, coronary vessels, etc. Considerable confusion is aroused by the fact that vasodilatation of certain intestinal blood vessels and activity of the sweat glands is accompanied by the release of acetylcholine from the sympathetic fibres supplying these structures. Just where these apparent discrepancies fit into the scheme of things is not yet apparent. However, adrenaline, and its associates the sympathins, appear to have a unity of action which surpasses in importance the discrepancies. Together they bring about throughout the organism those reactions which are required when extra demands are made by the environment. Thus we have—acceleration of the heart rate, dilatation of the coronary arteries, constriction of surface vessels, relaxation of the bronchiolar musculature, increased blood sugar from the liver, etc. All these things mobilize the resources of the organism and increase its efficiency.

Dale, in 1914, showed that the ester acetylcholine produced a "pronounced vagus-like inhibition of the heart, and various other effects of stimulating nerves of the cranial and sacral divisions of the autonomic nervous system."—

Loewi, in 1921, published his simple, unique, and illustrative investigation of the subject. Utilizing two isolated frogs' hearts, he perfused one with Ringer's solution. Then, after stimulating the vagus nerve, he found that the solution had acquired the property of inducing typical vagal inhibitory effects in the second isolated heart. The active substance formed was later shown to have the physical and chemical characteristics of acetylcholine.

Further evidence has accumulated to indicate that acetylcholine, as well as being the chemical mediator of parasympathetic impulses, is probably the chemical mediator of the motor nerves to skeletal muscle, and also the mediator at synaptic junctions. To complete the record it would perhaps be well to repeat that the sympathetic fibers supplying the sweat glands and uterus, as well as those causing vasodilatation of certain arterioles are cholinergic.

It rather upsets the pattern of things to find certain sympathetic fibres cholinergic. However, this and other apparent discrepancies might easily fall into the pattern of things if the whole subject of neurohumours were better understood. Indeed, the evidence obtained in exploring this field has warranted further investigation into the distribution of the sympathetic and parasympathetic components of the autonomic nervous system. An improved classification of this important part of the

nervous system might throw considerable light on the neurohumoural doctrine as well as many other fundamental physiological problems.

This theory of the chemical mediation of nervous impulses explains very nicely many of the reactions obtained upon the admission of certain drugs to the body. Eserine, or physostigmine, has an action almost identical with that of acetylcholine, simply by virtue of its inhibiting effect upon the choline esterase. Choline esterase is constantly present in the body fluids and breaks down the very active acetylcholine into the comparatively inactive choline, and acetic acid, almost immediately upon its formation. Obviously, if the activity of the esterase is curtailed, the ultimate effect will be the same as if the concentration of the acetylcholine had been increased.

Ergotoxine, which prevents the excitatory action of sympathetic impulses, interposes a barrier between sympathin E and the responsive mechanism in the cell.

Atropine, which annuls parasympathetic effects, is believed to act directly on the effector cell so as to prevent the action but not the liberation of acetylcholine.

A rather interesting phenomenon which should be mentioned in connection with this subject is the increased sensitivity of the effector cell to the chemical mediator after denervation of this cell. It was, indeed, the observance of certain reactions caused by this phenomenon which first presented a clue to the mode of mediation of the nervous impulse. The Vulpian effect, described in 1863, is a slow, gradual contraction of the tongue upon stimulation of the lingual nerve (ordinarily without effect) after the hypoglossal nerve has been cut and has degenerated. This is apparently brought about by acetylcholine released from cholinergic fibres in the lingual which are supplying the smooth muscle of blood vessels running to the vicinity.

Sherrington described a similar phenomenon in the muscles of the leg upon stimulation of the sciatic nerve after degeneration of the motor nerve supply.

It is now evident that it is the general rule for structures deprived of their nerve supply to be more readily responsive to their natural stimuli. The significant thing about this increased sensitivity, however, is that it is not specific for the natural stimuli. There is an increased sensitivity to other stimulants as well. Perhaps the best explanation for this occurrence is that the denervation renders the cells more permeable to stimulating agents.

The practical applications obtained from the experimental investigations of this subject are very suggestive. A profound, but temporary, improvement in cases of myasthenia gravis has been obtained with physostigmine, and more recently prostigmine has yielded even better results.

Further work on experimental animals has shown that acetylcholine will promote peristalsis and emptying of the bowel where it has been halted or impaired following anesthesia or due to exposure during an operation. The concentrations of the chemical mediator normally present are apparently insufficient to maintain peristalsis under these abnormal conditions.

It is still too early to predict the extent to which these findings may be applied clinically. In fact, the whole subject of neurohumours is still in the experimental stage. However the importance of the chemical mediator has firmly established itself in the scheme of things and it only remains to be seen what will be found along the many pathways opened up by this vast new field.

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COMPOUND FRACTURES

Part I - Introduction and Outline of Closed Plaster Technique

By M. E. W. GOODERHAM, '42

The purpose of this paper is to present a general method of treating compound fractures and to bring out certain points of difference. No attempt will be made to deal with fractures of special regions such as those of the jaw or cranium, so that it should be borne in mind that the suggested treatment must be modified as the circumstances indicate.

The plan is as follows:

I. A brief discussion of fractures in general and their complications.

II. The salient features with regard to care of a wound.

III. The treatment of compound fractures.

I. Fractures

The classical signs of fracture are:

1. Local swelling.
2. Ecchymosis.
3. Loss of function.
4. A local point or line of tenderness which may be elicited either by direct pressure or by pressure on the end of the bone involved.
5. Bony deformity. This may not be present as in the case of fracture of tibia without involvement of the fibula.
6. Preternatural mobility and crepitus. Further damage to the soft parts may be caused if an attempt is made to elicit these.
7. X-ray. Films should be made in antero-posterior, lateral, and oblique planes, with the joints in different positions, and should always show the whole length of the bone involved. In the case of a suspected fracture which is not revealed as such by the first X-ray, it is advisable to have another X-ray taken at the end of ten days. A line of rarefaction will be seen at the fracture line due to the rubbing of the ends of the bones upon one another.

A fracture may be one of three types, with displacement, without displacement, or compounded. The latter may be compounded either internally or externally.

The aim of treatment is reduction, fixation, immobilization, and restoration of function.

Reduction should be performed under an anaesthetic. This eliminates pain, relaxes the muscles, and reduces shock. It is effected by manipulation, by traction and counter-traction, or by operation, and thus may be either immediate or delayed.

Immobilization can be maintained by either internal or external fixation. The former method is by the use of screws, plates or nails, the latter by the use of circular plaster, splints, or traction and fixation apparatus.

Some complications of plaster immobilization are: gangrene, pressure sores, purulent dermatitis, skin blistering, oedema distal to the plaster, hypostatic pneumonia, renal calculus formation, and fat-embolism.[1]

The chief controllable causes of non-union are:

1. Failure to immobilize the fragments properly.
2. Mechanical or anatomical bars to healing.
3. Failure to maintain apposition.
4. The presence of infection or diseased states.

Watson-Jones says that "Provided that there is a continuous hematoma between the fragments, THE ONE AND ONLY CAUSE OF NON-UNION IS FAILURE OF ADEQUATE IMMOBILIZATION."

Restoration of function is concerned with the joints that are involved by the injury, or are immobilized through necessity, and the muscles that work these joints.

The question as to when to institute exercises is a much debated one, which the author can make no attempt to answer here. However, his feeling on the matter is nicely summed up by one of his clinicians in the remark, "Keep the part immobilized until union is obtained. Leave the attempts at early restoration of function to the bolder men and make them treat their own non-unions."

Other complications which must always be looked for are:

1. Shock—which varies with the extent of tissue damage.
2. Hemorrhage.
3. Embolism, either from a thrombus or of the fatty type.
4. Damage to other regions or organs of the body.
5. The extent of associated soft tissue damage. Locally there may be damage to vessels, nerves, joints, muscles, and skin. It must be pointed out that nerves may be either severed or contused. Dr. George Wilson says that he knows of no way of differentiating immediately other than by exposure of the nerve. It is essential that the extent of soft tissue involvement be determined before any treatment is instituted.

The indications for amputation are also a matter of difference so that only a suggested few are included here:

1. Destruction of the main blood-vessels.
2. Gross infection with gas-gangrene.
3. A part too badly mutilated to warrant orthopedic surgery.

II. A consideration of the factors which influence wound healing and means of utilizing them (4;13;15)

(i) Remove gross contaminants by washing wound with soap and water and then normal saline. Antiseptics should not be used in the wound because, (1;2)

1. The action of antiseptics is a specific one, or almost so.
2. The antiseptic is unable to penetrate sufficiently deeply into the tissues to reach invading bacteria.
3. The application of any noxious agent not wholly lethal will increase the resistance of the more resistant bacteria, so that they will become habituated to the chemical.
4. The toxicity of the bacteria is almost, if not equally as great to the tissues.

It is of interest to note that, in a series of experiments in which wounds were first debrided and then flushed out with either a bland solution or a solution of iodine and alcohol, the incidence of infection in 131 consecutive cases was 13.1% in the former and 18.1% in the latter.

The only necessary role of antiseptics is the preparation of skin surfaces before operation.

(ii) Do not introduce further contaminants. The strictest of sterile precautions must be observed.

(iii) Remove dead and damaged tissues and all foreign bodies, and avoid increasing the damage or the introduction of too much foreign body. This may be accomplished by a thorough debridement and the avoidance of mass ligature (some surgeons prefer silk because of its fineness as compared to cat-gut) and by using the most gentle technique in handling the tissues (13).

(iv) Hemostasis must be accurate and complete as the presence of an hematoma is detrimental.

(v) The use of chemotherapeutic drugs.

(vi) Special care with regard to the dressing of the wound as will be discussed later.

2. The tissues should be replaced and maintained in as nearly normal an anatomical position as possible. It is imperative that undue tension on ligatures be avoided.
3. The skin must be brought together with the wound edges everted.
4. Drainage measures should be instituted in the presence of pus or when large areas of tissues are bared, as in the case of a thyroidectomy.
5. The health of the local tissues must be maintained at its optimum, and for this purpose a resilient pressure dressing is advocated. The benefits to be derived from such are:
   - (i) The prevention of post-operative oozing.
   - (ii) Limitation of the amount of local oedema.
   - (iii) Giving of support to the local blood vessels.
6. Immobilization of the affected part. It has been shown that the spread of bacteria is chiefly via the lymph stream and that this is augmented by the application of heat and by movement (3).
7. Systemic measures.

(i) The fluid and electrolyte balance and the carbohydrate metabolism must be maintained. There must be proper elimination of body excretions.

(ii) The Vitamin C and protein levels of the body must be maintained at normal for good healing.

(iii) Systemic diseases must be treated if present. Especially is this important with nephritis, diabetes, acute and chronic anemia, and dehydration as they directly influence the progress of a wound.

(iv) The patient and the part must be put at rest as completely as possible.

A discussion of the common infecting organisms would be of value here. However it has been omitted for the sake of brevity Those interested may consult the bibliography for reference (11). Certain facts will be included in the summary which may be found here but have not yet been mentioned.

Let us now summarize the information gained so far.

1. Immobilization is essential for bone healing as movement of the fractured ends against each other will result in local atrophy and non-union. It also decreases the lymph flow from the affected area and thus prevents the spread of infection.

2. The functional activity of a joint is essential for good restoration of function, but exercises must be designed to avoid affecting the immobility of the fractured bones.

3. The use of warmth to the limb increases the flow of lymph from the affected part and should be avoided.

4. Debridement, by removing necrotic tissue, hematomas, and foreign bodies, prevents infection and hastens healing.

5. Gentleness is essential in the handling of the tissues, and the sutures used should be as small, as few, and as "unreactive" as possible.

6. The role of antiseptics is in the disinfection of the skin, and should never be used in a wound. Soap and water followed by normal saline is correct.

7. In frequent dressings of a wound avoid destroying epitheleization and granulation tissue, and thus prevent contamination of the wound.

8. Masks should be worn which cover the nose and mouth of *any* person treating the wound at *any* time, as should gloves. Efficient sterilization of instruments and dressings is essential. Irradiation of the field with ultra-violet light helps markedly in cutting down infection (11; 12; 24).

9. Gas-gangrene is treated prophylactically as is tetanus, or by the combined use of surgery, chemotherapy, and speific sera.

10. The local use of sulfanilamide does not adversely affect the final result in wound healing, but it combats and causes the destruction of many types of infecting organisms. Its use is preferably associated with that of specific sera (5-10; 14).

III. The treatment of compound fractures (1;16-23;25-31)

Under this heading the author will outline the closed plaster technique only, since details of other methods, as well as a discussion as to the relative merits of the different methods, will be found in a later issue of the Journal.

Closed Plaster Method

1. Anesthetize patient, put sterile dressing on wound, then wash entire extremity with water, soap, and a nailbrush. Shave all the hair, and prepare skin up to the edges of the wound with gasoline, ether, iodine and alcohol. Drape area involved.

2. Remove gross dirt from wound by washing with soap and water. Then lavage the wound with normal saline stream.

3. Make a complete debridement.

(i) Excise skin edges, remove all contused tissues unhesitatingly, cutting them back until healthy tissue is reached. Healthy muscle may be recognized by its colour, its ability to contract on stimulation with the forceps, and its capacity to bleed.

(ii) Open up the neighbouring cellular spaces affected by the contusion, and where necessary, incise the soft tissues, following up the cellular spaces in the depths of the wound. Remove any hematoma present.

(iii) Remove the majority of bone fragments that are completely denuded of periosteum or displaced, and all foreign bodies found at the site of fracture.

It is important that all foreign organic matter, such as clothing, be excised but pieces of bullet in inaccessible places may be left.

There is considerable disagreement as to the length of time after wounding that debridement is effective, and the extent to which it should be carried. It is agreed, however, that all main vessels and nerve trunks should be conserved during the debridement.

4. The fracture should be reduced immediately. The use of internal fixation is recommended by some here, and is also heartily condemned by other authorities as encouraging osteitis. If one is skilled in the use of internal fixation methods, and all other attempts to maintain good apposition fail, then one may justifiably use such a procedure. However, the author feels that such treatment should be avoided where possible because of the further unavoidable damage to the bone, and the introduction of a foreign body with the consequent reaction. Therefore he feels that infection should be cleared up before internal fixation devices are used.

5. When satisfactory reduction is attained powdered sulfathiazole should be introduced into the wound, followed by a packing of vaseline gauze.

6. The part and the two adjoining joints should now be immobilized in plaster. No window should be left to enable the wound to be dressed. The latter factor invites infection and the window permits a slight mobility, local edema, increases local discomfort, and rupture of the surrounding shell of lympathics and capillaries.

Change of plaster is necessitated by the smell. The first change is at 15 days, the second 30 days after, and other changes when needed until union is complete. All changes should be effected in the operating room with sterile technique until the wound is healed.

Danger signs that should be constantly watched for are:

(i) Progressively increasing pain or discomfort at the site of the wound.
(ii) Rising temperature and general malaise.
(iii) Edema of the distal portion of the extremity.
(iv) Inability to move the distal parts.

When any of the above occur the plaster should be removed and appropriate measures taken.

7. Some authorities advocate the immediate closure of the wound if the shape of the wound permits. This should never be done if the wound is over six hours old as any contaminating organisms present will have become established by that time. It also increases the danger of non-drainage should there be infection present, as is most likely. Such procedure should only be used with suitable wounds and by a surgeon of mature judgment.

8. In cases where deep cavities are present drainage must be arranged by the insertion of sterile vaseline gauze or rubber tubes. These should be buried under the plaster and retained until the first removal of the cast. No complication can be attributed to the drainage, but a retained discharge, the result of bad drainage, may bring about disaster.

Plaster of paris is the most efficient form of splint. However it is conducted, extension can never be as efficient a means of immobilizing a broken bone as a plaster-cast. The pull transmitted to the muscles surrounding the fracture is sometimes of value in maintaining the position of the bone ends, but in air-raid casualties, the gross destruction of muscle produced by aerial bombs militates against this advantage. The treatment by traction, even if as efficient for bone as the plaster cast, gives none of those requirements essential for the immobilization of the soft tissues. Traction is also necessary in oblique fractures.

The immediate effects are:

1. Rapid recovery from the severe local pain and shock.

2. Temperature chart shows a constant rise on the days immediately following the application of the plaster. There is usually a rise in temperature each time the cast is changed.

3. The local resistance may remain favourable, yet there will be glandular swellings in the axilla or groin.

4. The wound should be comfortable. No sensations of tension at the site of the wound should result.

It is interesting to note that Trueta did away with any treatment for gas-gangrene unless it was definitely established when treatment was instituted.

A summary of his Catalonia experience is of interest here.

Number of cases.....	1673	
Good results.....	976, or	90.9%
Bad results.....	91, "	8.6%
Deaths.....	6, "	0.5%

Immobilization in plaster should be maintained until there is X-ray evidence of bony union. Check X-rays should be made at the end of two and six months to be sure that there is no rarefaction taking place.

Conclusion

There are many factors in the treatment of compound fractures that have not been discussed for the sake of brevity. The salient features with regard to the treatment of wounds and fractures have been reviewed. It is to be hoped that interest in this problem has been stimulated to the point of forming opinions of one's own and it is for this reason that the author, although handicapped by a lack of practical experience, has been dogmatic about points of much difference.

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Book Section

THE DYNAMICS OF INFLAMMATION

A REVIEW OF THE BOOK by G. G. CAUDWELL, 4T3

Quite recently there came to hand an interesting monograph by H. V. Menkin, the title of which forms the capital of this article. Its very name invited further scrutiny and indeed described in the best possible fashion the very nature of the process with which it dealt. Had the title been—the principles of Inflammation,—its attractiveness would have been lacking and the impression of its activity lost.

Inflammation may be defined as the response of a tissue to irritation in an endeavour to localize and dispose of the irritant and institute repair. Such an inflammatory response is not static but dynamic—a sequence of interrelated events which may be traced step by step and the role of each so determined. These events are several in number, which for the purpose of discussion must however be presented individually at the risk of distracting somewhat from the impression of their interdependency. The events are these:

I. *Increased passage of fluid through the capillary wall.*

This phenomenon was observed experimentally on the introduction of chemical or bacterial irritants into tissues of animals. It was believed to be due to (*a*) A local vasodilatation with an increase in capillary pressure, the probable result of a local axone reflex, which would so favour filtration. (*b*) An alteration in the permeability of the capillary wall. This conclusion was substantiated by the injection of Trypan Blue intravenously into animals having a local area of inflammation present. The dye was found to have concentrated in the extracapillary spaces at the inflammed area. Local application of heat or mustard plaster caused a similar accumulation of the dye.

The mechanism of this increased capillary permeability presents a most controversial subject. It has been widely accepted in the past that this reaction was due to the liberation of a substance called Histamine from the injured tissues or a substance closely akin to it. However Menkins found that the concentration of Histamine in an inflammed area was essentially the same as that found normally in the tissues, as evidenced by their respective actions on the contractility of the guinea-pig uterus. He isolated from inflammatory exudates an active fraction which he compared with Histamine and found it lacking in the properties characteristic of the latter. This fraction was termed the permeability factor and called Leucotaxine as it was capable in itself of producing the sequence of inflammation. It induced a prompt increase in the permeability of normal capillaries and an immediate leucocytic migration. The factor was not a protein but believed to be an intermediary breakdown product of protein metabolism—possibly belonging to the group of relatively simple polypeptides and being formed as the result of an interference with normal protein catabolism due to the presence of the irritant. It produces little tissue injury but affects cell division which may have a direct bearing on the endothelial cells of the capillary wall.

II. *The Concept of Fixation*

One of the prime requisites of the Inflammatory process is the localization of the irritating factor, or in the limitation of its dissemination. Thus by delaying the spread of the irritant into the blood stream, the inflammatory reaction protects the organism as a whole but at the expense of local injury. Such

action is almost immediate occurring readily in some 30 minutes and so giving time for the assembly of leucocytes and subsequent phagocytosis. This fixation or localization of the irritant, in Menkin's view is dependent upon two facts. (*a*) The formation of a mechanical barrier composed of a fibrinous network, derived from the fibrinogen of the plasma, which so walls off and endeavours to isolate the irritant from the rest of the body and (*b*) the blockade of the lymphatics by a fibrinous network and adherent leucocytes. Such obstructions interfere with drainage from the area and so limit any spread of the irritant along these channels. It also is a factor in the development of the inflammatory oedema.

Such conclusions are not without experimental verification which bear presentation. Menkin injected a bacterium B. prodigiosus into an acutely inflammed area and found that the bacteria were retained in situ, and failed to spread into the tributary lymphatics. Cultures were taken from regional lymph nodes and compared with those taken from nodes draining a normal area into which the same bacterium had been injected and in every experiment the number of colonies gained from the latter was greater than that gained from the former case. The same results were found when Trypan Blue particles were used. Thus Fixation is a protective mechanism which plays a definite role in immunity.

The fact that certain bacteria are more invasive than others offered a challenge to this concept of fixation. Could the tendency of styeptococcal infection to spread widely and rapidly while that of the staphylococci remains localized be explained in the light of these new facts? Menkin found the answer in the results of his investigations. He experimented with staphylococcus aureus, streptococcus haemolyticus and the pneumococcus. type I, and in each case produced an area of inflammation into which was injected Trypan Blue whose appearance was noted in the regional lymph nodes. With staphylococcus aureus, one hour after infection with the bacteria, the dye failed to reach the regional lymph nodes, due to the prompt lymphatic occlusion. Streptococcus haemolyticus required 48 hours following the cutaneous inoculation before there was lymphatic occlusion, while the pneumococcus type I case required some 20 hours before there was lymphatic blockade. Thus the rapidity and the intensity with which the lymphatic blockade is induced may well determine the invasiveness of pathogenic bacteria. In the first instance there was early fixation and localization of the irritant with, however, extensive local destruction of tissue. In the second, fixation occurred late, long after the bacteria had invaded the lymphatics and widely disseminated. There was a minimum of local destruction, the bacteria having concentrated on a wider field with predominantly systemic effects.

The importance of the mechanism of fixation cannot be emphasized more strongly than by bringing to mind those quite avoidable tragedies which have resulted from untimely interference with, or trauma of, this protective inflammatory barrier and blockade, which so allowed the spread of the irritant and the opportunity to wreak havoc in a more vital area.

III. *The Cellular Sequence in Inflammation.*

In an acute inflammatory reaction, there is an initial infiltration of polymorphonuclear leucocytes followed by an eventual replacement by macrophages, the change being dependent on the production of a local acidosis in the inflamed area. The local hydrogen ion concentration is dependent upon the rate of lactic acid formation as the result of a disturbed or imperfect carbohydrate metabolism due to the presence of the irritant. The polymorphonuclear leucocytes are more sensitive to an acid condition than are the macrophages and are so injured and destroyed. However below a pH 6.8 all cells are injured and frank suppuration intervenes.

IV. *The Mechanism of Leucocytosis*

It has been believed for some time that following extensive injury to tissues, some substance was released from the tissues which brought about a mobilization of leucocytes with a consequent increase in their number in the circulation. This substance was called the Leucocytosis - promoting factor by Menkin who found it to be quite divorced from Leucotaxine. It was found to be present in exudates but its exact nature is quite unknown. probably being a globulin or a pseudo-globulin. The factor exerts its effect primarily on the haemopoetic tissue in bone marrow causing an outpouring of immature polymorphonuclear leucocytes with a shift to the left in the Arneth Count.

V. *The Migration of Leucocytes into the Inflamed Area*

Such a mechanism as this has never been satisfactorily explained. The hypothesis that the migration was referrable to changes in surface tension or to difference in hydrogen ion concentration is merely inference, there being little direct experimental evidence to substantiate them. Histamine fails to produce such a response and so its release from injured tissue is of no importance in this respect. However, with Leucotaxine, Menkin found the lumina of vessels crowded with cells 15 to 20 minutes after its injection into the skin with many adhering to the endothelial wall. Indeed in 30-40 minutes the extra-capillary spaces contained many leucocytes. Further, polymorphonuclear leucocytes when introduced into an area in which a crystal of Leucotaxine is present, immediately cluster about it but fail to do so with a carbon particle. Thus this active material Leucotaxine, which can be crystallized, is capable of reproducing the basic sequence of the inflammatory reaction.

It might be well, in conclusion, to visualize the Dynamic Action of Inflammation in the light of several recapitulations. The reaction of tissues to injury is essentially a disturbance in local metabolism with the formation of Leucotaxine which in turn induces both increased passage of fluid from the capillaries and the migration of leucocytes from the capillary wall. Thus is there a local concentration of the fluid and cellular elements of the blood resulting, not only in the localization of the irritant by the formation of a mechanical barrier of fibrin and a lymphatic blockade but also in the disposal of the irritant by phagocytosis.

Feature Section

J. B. ROBERTS, Editor

STUDENT OPINION

By R. G. BELL, '43

This article is an attempt to correlate some of the opinions of medical undergraduates on problems pertaining to the practice of medicine and its application to social needs. That these problems are recognized and intelligently discussed by students, can be discovered by anyone who cares to find it out. The fundamental purpose of the article is not, therefore, to present any personal set of beliefs but to stimulate further discussion and, if possible, initiate definite action.

The problems to be mentioned here are those which to be solved require a united stand by us as students and later as doctors. They include such topics under general discussion as state medicine or health insurance, medical students and the army, preventive medicine and its possible effect on general practice, malpractice, lack of sufficient undergraduate activities, broadening of medical education, and many others. In this article only a few of these will be considered.

In his article, "The Medical Student of Today and his Relationship to the Future of Medical Economics," appearing in the October issue of the MEDICAL JOURNAL, Dr. J. A. Hannah discussed ably and thoroughly the problems of state medicine and health insurance as they are related to us. It is important that we understand more concerning these subjects and that we be given the opportunity to discuss them together. In this regard we could go one step further and seek to determine how the many new discoveries and developments in preventive medicine can be incorporated into any of the plans he has mentioned.

Many of the latest developments have occurred within the last few years and we who are soon to graduate and who have been fortunate enough to be in college at the time of their discovery should shoulder the biggest share of responsibility in adapting them for general use

What is bound to concern us sooner or later is that if we are to practice in some new manner, that manner should be decided by doctors rather than lawyers or business men. It is unlikely that anything can be done for the present that will take the matter out of their hands and into ours, but there is nothing to prevent medical men from organizing themselves, analysing the whole problem, and in time presenting a plan that will be of much greater value both to themselves and to those who require their services. Judging from the efficiency with which other state problems are met, it appears inevitable that, regardless of the form that the new Bill may take, it will require considerable remodelling by suitably trained men.

Another problem that has stirred students to a pitch of unusual eloquence is that of malpractice and incapability on the part of many who still retain the right to call themselves doctors. For example: a text-book picture of subacute bacterial endocarditis was diagnosed by a fourth year medical student who discovered that the physician in charge had called the condition first catarrhal jaundice, then typhoid fever, and was also collecting for vitamin B injections. Naturally, nothing could have been done to cure the patient, but it certainly does not seem right that the family should receive a bill—even for the vitamin injections—from such a man.

Another doctor near Toronto sent a woman to the Toronto General Hospital

with a note attached to the effect that he was sure her prostate was not involved since he had examined it himself.

The list could be continued indefinitely. Are we sufficiently proud of our profession, and sufficiently aware of our social responsibilities to take decisive steps toward the eradication of such malpractice? Do you think it possible that we could include a plan for the prevention of this in future in our scheme for the reconstruction of medical methods? Would either the periodical examination of all doctors, or the abolition of private practice in favour of numerous small clinics solve the problem?

Now we come to the question of our own education. Strange as it may seem, most consider that rather than getting too much they receive too little. Not that there is any feeling of insufficiency in so far as our medical training is concerned—far from it—but in other realms which would help us decide how best to apply our medical knowledge once we have acquired it. This in fact may at the moment be playing a considerable part in the confusion of prevailing methods and the inability to form any general suitable program. We not only must earn our living as doctors but should be able to play a more strenuous and responsible role in all matters of national significance. We are by nature suited as well as, or better than, other professions to take a leading part in solving problems outside of a strictly medical sphere. However, we are at present handicapped firstly by lack of time and secondly by lack of education beyond that which is of a purely medical nature.

Some students wonder why doctors should not be well represented in both the Dominion and Provincial Government Houses. Do you consider this to be either possible or desirable?

Philosophy, ethics, economics, and political science represent the subjects which we lack, and could certainly use. We study physiology and psychology, but fail to carry through to the next logical step, namely, the study of sociology.

Equally important is a practical knowledge of what the various levels of society do and think about—how much they earn and what type of work they do to earn it. We should understand something of labour unions from the labourer's viewpoint as well as business associations from the employer's side. Modern trends and experiments in education and social readjustment, now under way in United States in particular, should constitute part of our knowledge.

Again, we run into the obstacle of insufficient time in which to acquire all of this information. Any comprehensive scheme to include these and other subjects in a medical education can only evolve gradually through the united efforts of medical students, our Faculty, practising physicians, and public and high school authorities.

More than one student has wondered whether it might be desirable to split the present medical course into several narrower specialized fields with additional education in more general lines. Their argument is that because of the wealth of new medical discoveries each year it will soon be impossible for any one person to absorb it all. Certainly some of us have enough trouble with it even now. We as students can do something, however, about obtaining at least a nodding acquaintance with these unfamiliar subjects, and a suggestion in this regard is advanced later in this article.

To achieve anything towards a solution of any of these problems it is first necessary for the students to assemble and discuss them. Furthermore, the extra-curricular life of every medical student should be such a vital part of him that he will seek in later years to keep in touch with it through various alumni associations.

Let us next try to analyse the causes of the lack of more extra-curricular activities and the generally poor school spirit.

1. We are situated not in a college town but in the centre of a large city. It requires less effort to find outside entertainment than to provide it through college functions. Those Toronto stu-

dents who have been connected with Camsi agree, however, that the school spirit at McGill is better than at Toronto —consequently, the size of the city cannot be so important.

2. The student body in medicine is made up of approximately twelve nationalities and half as many religions. They come from relatively poor to relatively wealthy families. In some instances neither home training, previous schooling, or even religious teaching has adequately prepared us to work shoulder to shoulder with members of other races, religious groups or income levels. A glance at any newspaper or magazine will show us that we are in no way unique in having such a problem. England was surprised to find that in dissolving social partitions as a necessity of home defence it entered into a welcome, interesting, and constructive adventure in human understanding. At no time in history has it been so necessary for everyone to understand that racial and like prejudices are obsolete and for each individual it is a personal responsibility.

3. Again, we must consider that one of the chief causes for lack of enthusiasm regarding outside functions is that students do not think they can spare time from their studies. This very real problem should receive the close attention of the staff as well as the students. Perhaps it is the price we pay for belonging to the medical school with the highest rating on the continent.

There are numerous other reasons for the lack of any concerted action by medical students, but no purpose could be answered by prolonging this part of the discussion.

The following suggestion is submitted for your consideration.

Since the student body is so large and unwieldy, let us divide into groups or clubs. We could have a music club with, for example, a male choir unequalled on the campus. Dramatics, art, photography, ski, skating, and bridge clubs are all possibilities. Since we do not study subjects like philosophy, we could have philosophy, sociology, current history, and others of this nature. The suggestions as to what clubs should be formed should come from the students themselves, preferably in writing to the Medical Society office. Members of the staff and in particular the younger doctors on the staff of the various hospitals should be invited to join. It has always been an unfortunate feature of large universities that many students never have the chance to know their professors personally.

It is further suggested that these clubs meet every two weeks and that the Medical Society undertake the responsibility to provide suitable meeting places. Also it seems wise that each meeting begin about six p.m. with a dinner—that arrangements be made to provide these meals at a reasonable cost—and that the ensuing meeting of the music club or whatever it may be close not later than 8 or 8.30 p.m.

Even though this at first may seem contradictory, there will be no necessity for anyone to feel that he or she must concentrate an already weary brain on ponderous matters of vast social significance, etc. As was pointed out earlier, students in medicine are already aware, interested and well informed for the most part on all these matters. It will only be necessary to provide them with a suitable, enjoyable means of meeting together and all such problems will naturally crop up in the conversation. What is chiefly important is that these clubs do not cease entirely to be a part of us after graduation.

Last year there was a considerable surplus after the expenses of the Meds At-Home were paid. Let the Meds At-Home in future be a means of providing funds for the operation of the various clubs. Every student should belong to at least one club and should work hard to see that the Meds At-Home each year is a real success.

Within a year from the time these clubs are formed we should be in a position to have our Daffydil Night returned—under new colours—acceptable to everyone.

Our open meetings could be in charge of two of the clubs—one-half hour to each. Furthermore, they should be held in the afternoon, during school hours,

e.g., from 3.30 until 5.00 o'clock, in a place large enough to accommodate all eight hundred students. These meetings, as in the past, could be held once a month, and surely this phase of our student life is as important as an extra lecture a month for each year.

It would be well to have not only the Medical Society as a parent organization but also the Camsi (Canadian Association of Medical Students and Internes), and in this way correlate our activities with those in other medical schools. Suggestions from the clubs should reach both bodies.

We have the framework on which to build,—in undergraduate years—the Medical Society and Camsi; in post-graduate years, the Medical Associations and the College of Physicians and Surgeons. Nothing new is added but a co-ordinated movement to make all of these organizations function more effectively.

Finally, it is, above all, vitally necessary that as students we enjoy meeting one another through common interests, if later, as doctors, we are to work together effectively on matters of common weal.

MEDICAL ECONOMICS SERIES OF THE CANADIAN MEDICAL ASSOCIATION

BULLETIN NUMBER 3

(*Editor's Note:* Bulletins Number 1 and Number 2 were printed in the April, 1941, issue of the JOURNAL.)

VOLUNTARY vs. COMPULSORY HEALTH INSURANCE

The conditions necessary for the successful conduct of any health insurance plan, which were discussed in Bulletin No. 2, apply with equal force whether the plan be *voluntary* or *compulsory*.

Voluntary health insurance societies have expanded notably during the last 140 years, and—under careful supervision—have in large measure filled the needs which prompted their establishment. In many countries, however, governments have not been content to permit this voluntary co-operative movement to grow naturally. Commencing in Germany in 1883, a wave of governmental action has swept over many lands, and *compulsory "Social Insurance"* has been developed widely.

These compulsory "Social Insurance" plans may be defined as

> "methods of securing money income, or other benefits in cash or in kind, on the principles of insurance, to workers and their families in the cases of sickness and invalidism, old age, death, and unemployment, when the State, in whole or in part, undertakes the creation and administration of such schemes, frequently prescribes the bases upon which employers or employees, or both, are obliged to contribute, and often assumes the ultimate responsibility for the financial sufficiency of the plans".

Their chief characteristic is a form of governmental regimentation. A little contemplation will show clearly that governmental operation of these insurance schemes places very wide powers in the hands of government officials. A larger number of people are insured, of course; but against this must be set the disadvantages of regimentation. It should be noted, morever, that the term "Social Insurance" really should not be reserved for describing only these compulsory governmental plans—for *all* insurance, whether voluntary or compulsory, is "social" in the truest sense.

Voluntary or Compulsory Insurance?

The advantages and disadvantages of voluntary and compulsory insurance may be summarized as follows:

The ADVANTAGES of VOLUNTARY insurance lie in

(i). The preservation of individual personal liberties;

(ii) The real interest which members of any voluntary co-operative effort naturally feel in protecting and enlarging the usefulness of their own endeavours;

(iii) Voluntary plans can be made to cover *any* economic group so long as the necessary contributions are paid and the conditions for insurance are fulfilled; and

(iv) Voluntary insurance is simply a method of *sharing* burdens—there is no attempt to make other people responsible for the individual's own problems.

The DISADVANTAGES of VOLUNTARY insurance are that

(*a*) Only some people in any community are sufficiently far-seeing to protect themselves by joining an insurance plan;

(*b*) Some low wage-earning groups cannot afford to pay the necessary contributions; and

(*c*) Voluntary plans may encounter financial difficulties unless they are carefully and wisely administered, and have competent actuarial advice and supervision.

The ADVANTAGES of COMPULSORY governmental insurance are that

(i) People not ordinarily interested are required to come under the protection of the government plan, so that the groups covered are often much larger;

(ii) So far as the insured person is concerned, the financial sufficiency of the plan is assured, for the government, in case of insolvency, usually must provide the necessary funds; and

(iii) Certain contributions are obtained from many of the lower wage-earners, which otherwise it is said might be spent "unwisely," and almost certainly would not be used to purchase insurance coverage.

The DISADVANTAGES of COMPULSORY governmental insurance are that

(*a*) The governmental regimentation which is inherent in any compulsory plan may be felt, in many cases, to be an unwarranted interference with personal liberty;

(*b*) The plans are based on the idea of making the employers and the general taxpayers responsible for about two-thirds (usually) of the costs of the scheme, so that the employee thus *shifts* a part of his own economic problems on to the shoulders of other persons; namely, the employers and the public at large;

(*c*) The plans consequently have a tendency to develop artificial economic pressures and malingerings of many kinds, with the object of obtaining personal advantages over those other persons who are compelled to contribute to the costs but derive no benefits; and

(*d*) The plans generally cover only certain specified employees, and then only while they earn not more than some arbitrarily pre-determined figure (such as $1,800, or $2,000, or $2,400 per annum); all others are excluded, whether they earn much or only a very little more, or nothing at all.

BULLETIN NUMBER 4

THE DEVELOPMENT OF HEALTH INSURANCE IN CANADA

One of the most important questions confronting the doctor of to-day concerns the position which he would occupy in any voluntary or compulsory health insurance plan.

Cash Benefits vs. Benefits-in-Kind

Health insurance plans are of two kinds—those which give *cash benefits* to their members during sickness, and those which give *benefits-in-kind* (medical care, surgery, hospitalization, drugs, etc.).

Under the CASH BENEFIT system the doctor usually has to certify as to the character and duration of the illness. His certificate is then scrutinized by the claims department of the insurance plan to verify the admissibility of the claim. The doctor receives payment for his services *from the insured person* (not from the officials of the insurance plan).

When the plan gives BENEFITS-IN-KIND, however, the doctor's position is different. He must again certify the illness, and his certification will be scrutinized; but he receives his payment *from the officials of the insurance plan* (not from the insured person). When the officials of the insurance plan are medical men it will therefore be seen that the doctor will have to deal only with medical men in obtaining approval of his certification and payment of his account. This feature of medically-controlled plans which give only benefits-in-kind is often held to be one of their chief advantages, since "lay interference" is eliminated.

It is not wise, however, to be dogmatic on these questions, for all of them can be solved only by *co-operation* between the three main groups concerned—the insured members, the certifying doctors and others who provide the services, and the financial administrators. It must be remembered that "not in any type of plan is it possible to remove from the insured the obligation to be honest, or from the doctors the duty of certifying claims, or from the administrators the responsibility of supervision." An insurance plan, moreover, should never be thought of as a method by which some special group can gain "control," whether of procedures, certifications, or modes of payment—for the essence of insurance is co-operative "sharing," which ought to be kept free from prejudices, ulterior motives, and the quest for power.

Experiences in Canada

The restrictions just enumerated are important in their bearing on the development of methods for meeting the costs of medical care in Canada. *The problem is essentially provincial*, for under the British North America Act (which in this respect was endorsed by the Rowell-Sirois Commission's Report) health insurance falls within the subjects for provincial legislation covered by section 92 (concerning "property and civil rights"). No compulsory governmental health insurance scheme, however, has yet proved to be acceptable in any part of Canada, although much controversy was aroused a few years ago by the proposal of such a plan in British Columbia.

The problem being thus provincial, it is not surprising to find that, so far, each province has adopted methods suited to its own special circumstances.

Thus in *British Columbia*, since the compulsory health insurance proposal was withdrawn by the Government, an experiment is being tried with a voluntary insurance plan giving benefits-in-kind (for groups of employees earning not over $2,400 per annum each) in Greater Vancouver and New Westminster.

In *Alberta* a compulsory scheme was suggested in 1935 by which benefits-in-kind would be provided for *all* the people of the Province—but this also has now been abandoned.

In *Saskatchewan* a wide development has occurred in the "municipal doctor" plan, and through legislation designed to encourage a form of municipalized medicine, sponsored and supervised by the Provincial Government—in effect a kind of "state medicine" (not "insurance"). The establishment of voluntary insurance plans giving benefits-in-kind has also been considered in several different places.

In *Manitoba* the "municipal doctor" plan has likewise been prominent, and surveys of medical costs have been undertaken in connection with the City of Winnipeg Medical Relief Scheme, and in certain rural areas.

In *Ontario* the developments have been featured by the establishment in ten centres of a voluntary insurance plan giving benefits-in-kind (to any eligible person without salary limit) through Associated Medical Services, Incorporated, and by the Hollinger Employees' Medical Services Association at Timmins, and by another plan in the Windsor area. The Ontario Medical Association since March, 1935, has also been administering a government-sponsored plan for providing medical care to relief recipients throughout the Province.

In *Quebec* the development of "health units" has progressed widely — these units in 1939 existing in 53 of its 90 counties. They consist ordinarily of a medical health officer, sanitary inspector, and others, and bring to the country districts advice and supervision in epidemiology, maternal hygiene, school conditions, etc. A Social Insurance Commission in 1933 reported in favour of subsidized voluntary insurance rather than a compulsory system.

In *the Maritime Provinces* a form of health insurance, called "mining contract practice," has been operating amongst the mining companies' employees for many years.

Hospital Care Plans

In addition to the voluntary plans, like the Associated Medical Services, which give a comprehensive list of benefits-in-kind, such as medical and surgical care (both in the home and hospital), consultants' services, anaesthetics, x-ray, drugs, etc., and semi-private (or an equivalent sum towards) hospital accommodation (but not exceeding $3.50 per day), a notable growth has taken place recently in Canada, as in the United States, in plans of *hospital insurance only*. The benefits provided by this hospitalization insurance usually cover simply the costs of semi-public or semi-private hospital accommodation (or an equivalent allowance towards a private room) for not over a limited number of days, with general nursing care, operating and case room service, laboratory and x-ray, etc. (sometimes not exceeding a stated value), and

ordinary drugs and dressings while in the hospital. Such plans evidently include only some of the easily defined elements in the costs of serious illness; although meeting one of the major financial problems of sickness, they make no attempt to include the more elusive and widely-varying costs of the general practitioner, specialist or consultant, surgeon, special nurse, etc., which generally are also covered by the complete voluntary medical care insurance plans.

Any comparisons of the actual cost figures of existing plans—whether of comprehensive medical services insurance, or hospitalization insurance only —must be made with caution, for it will generally be found, on careful examination, that the various plans offer somewhat different kinds of services and operate under differing conditions, which have a marked effect upon the results obtained and the costs emerging. A discussion of these costs would be too long for inclusion here; it will therefore be held over for a later Bulletin. If the information should be required, however, a summary may be found in articles IX and X of the publication entitled, "The Canadian Medical Association and the Problems of Medical Economics"—particularly in pp. 68-70 of the latter—to which reference has already been made.

Abstracts

D. P. BRYCE, Editor

Contributors { R. J. Wilson, J. C. Mickler, G. C. Caldwell

The Toxemias of Pregnancy and the Management of Parturition

Mussey & Hunt, Rochester
J.A.M.A., Oct. 18, 1941

This paper presents firstly the classification of toxemias of pregnancy as adopted by the American Committee on Maternal Welfare, which distinguishes mainly between those chronic conditions not a result of the current pregnancy and the acute hypertensive toxemias directly dependent on and peculiar to the pregnant state.

Their Classification is as follows:

Group A. Disease not peculiar to pregnancy, i.e. that aggravated by pregnancy and producing symptoms before the 24th week.

I. Hypertensive disease:
  (*a*) Benign, mild severe;
  (*b*) malignant.
II. Renal disease:
  (*a*) chronic vascular nephritis or nephrosclerosis;
  (*b*) glomerulonephritis
    (1) acute
    (2) chronic
  (*c*) nephrosis
    (1) acute
    (2) chronic
  (*d*) other forms of renal disease.

Group B. i.e. Diseases dependent on or peculiar to pregnancy presenting symptoms after the 24th week.

I. Preeclampsia:
  (*a*) mild i.e. B.P. < 160 and 100;
  (*b*) severe, usually with retinal changes.
II. Eclampsia:
  (*a*) convulsive;
  (*b*) non-convulsive i.e. coma with P.M. findings typical of eclampsia.

Group C. Vomiting of pregnancy.
Group D. Unclassified types.

The authors go on to discuss management of these cases in labour. In the severe types of Group A termination of pregnancy is advised and in Group B conservative treatment as taught in this school is advised.

D. P. B.

Chemotherapy During Pregnancy

Heckel, M.D., Rochester
J.A.M.A., Oct. 18, 1941

The widespread use of these drugs raises at once the question of its effect on the foetus. It is demonstrated that the drug passes through the placenta and its concentration in foetal blood rapidly approximates that in the maternal blood. Later the baby may while feeding on the breast be subjected to chemotherapy but the amounts obtained in this way are negligible.

Work with experimental animals indicate that the foetus whose mother received the drug had less chance of survival, and in the cases seen in hospital at least one infant demonstrated severe anemia probably caused by the drug. It would appear, therefore, that its administration is not without danger to the foetus. Full therapeutic doses should be given if necessary, however, because there is no relation between size of dose and damage to foetus.

D. P. B.

Pneumonectomy

Frank Berry, N.Y.
Annals of Surgery, July, 1941

Pneumonectomy as a surgical procedure is quite a recent development, and

as such is of course open to a good deal of criticism. The authors emphasize the necessity of differentiating the different operative procedures used and the pathological processes involved in any report or series of cases. Finally it is shown that the operative mortality for exploratory thoractomy and pneumonectomy is less than that for exploratory celiotomy and gastric resection when cancer is involved in both cases.

It is necessary to distinguish between "complete pneumonectomy" where there is removal of the whole lung with individual ligation of the hilar structures within the mediastinum and removal of mediastinal lymph glands, from "subtotal or incomplete intrapleural pneumonectomy" where part of the lung alone is removed, and where the mediastinum is not entered. With bronchogenic carcinoma, only those cases without mediastinal involvement should be attempted and in all cases a "complete pneumonectomy" done. Tuberculosis should be dealt with by the "complete" operation but "intrapleural pneumonectomy" is probably safer for the suppurative lesions.

The authors also point out the prevalence of circulatory anomalies at the hilum as a point to be remembered and studied. They carry out extensive physiological research both post and pre-operatively to

1. Evaluate the surgical risk.
2. Gain insight into the respiratory and cardio-respiratory status of the patient's post operatively.

Such studies include measurements of lung volume, breathing capacity, efficiency of ventilation and a study of circulatory condition by the venous pressure infusion test.

D. P. B.

Applicability of Experimental Results to the Shock Problem in Man

By Wiggers of Cleveland

J.A.M.A., Oct. 4, 1941

Here is discussed in a general way the experimental approaches to the problem of shock. It has been the criticism of this work that the shock thus produced does not simulate clinical conditions and the interpretations do not agree with clinical observations.

It is necessary to have criteria to indicate that a condition has been produced which is similar to human shock. For obvious reasons it is difficult to formulate such criteria with animals. It is suggested that the best criterion of shock in animals and man, is the coexistence of a reduced cardiac output and hypotension. The writer does not believe that a diagnosis can be made from blood studies before the above dynamic conditions exist, because such conditions are necessary before an irreducible circulatory failure can develop.

The experimental procedures used to produce shock can be divided into three groups.

A. Haemorrhage, crushing injuries, intestinal obstruction, etc.

That is procedures comparable with those naturally producing shock. That haemorrhage alone can produce shock is debatable, but the author claims that if blood is withdrawn so that respiratory failure does not occur, then a state of circulatory failure develops which is not alleviated by return of all the blood lost.

B. Prolonged hyperthermia, prolonged freezing, etc.

These procedures are unlikely to occur in man and have been developed in an attempt to produce the condition with more consistence than possible from Group A.

C. Injection of fat emulsions, excessive pulmonary ventilation, compression of the inf. vena cava, prolonged compression of aorta or stimulation of afferent nerves, toxic factors, etc.

These procedures are never produced by natural causes. However, such investigators have explored clinical clues and produced theory which has led to a great advance in the study of shock. For example, working with excessive pulmonary ventilation Henderson in 1908 formulated the idea basic to our current conception of the condition. Namely the

conception of the venous pressure as the "fulcrum" of the circulation and with failure of the fulcrum follows inadequate filling of the heart, and falling arterial pressure in spite of constriction of the arterioles.

Again investigators compressed the vena cava and showed that the blood thus distending the venous system and the fluid lost from serous surfaces were responsible for diminished venous return and a condition of shock. These experiments were precursors to later experiments showing that blood is concentrated in shock with a diminished volume, and also that sufficient blood or plasma could be drained into a traumatized area to initiate progressive circulatory failure.

Also original experiment with retardation of capillary flow from the arterial side, led to the peripheral vasoconstriction followed by anoxia and increased permeability theory, which is still held by some to-day.

Work with histamine although not yet accepted may still lead to the involvement of some toxic factor. Thus the author believes he has demonstrated the value of what to some appear to be abstract experiments.

He himself believes that shock is initiated by a decrease in effective circulatory volume but that the operation of some precipitation factor or the failure of some compensatory mechanism is necessary to cause the irreversible state of circulatory failure which occurs. Such determining factors may have to do with the capillaries such as creation of irreversible damage so that they no longer hold fluid, or may have to do with other structures such as:

(*a*) failure of reflexes normally stabilizing blood pressure;

(*b*) failure of blood mobilization;

(*c*) failure of processes aiding venous return;

(*d*) or finally, failure of the proper action of the myocardium itself.

D. P. B.

The Causes Underlying the Recent Increased Incidence of and Mortality from Tuberculosis in Glasgow

Stuart Laidlaw, B.Sc., M.D., D.P.H. D.P.A., and
Duncan Macfarlane, M.B., Ch.B., D.P.H.
(From the Public Health Department, Glasgow)

British Medical Journal Sept., 1941, p. 436

For the five years preceding the outbreak of war in 1939, there seemed to be a stabilization of the incidence of and mortality from pulmonary tuberculosis in Glasgow at around 1,650 notifications and 960 deaths per annum. In 1940 there were 1,908 notifications and 1,177 deaths, a rise of 250 notifications and 200 deaths. These figures are being maintained in 1941. The increase is almost entirely between the ages of 15 and 45 in males and 15 and 35 in females. Both sexes show an all-round increase of about 20 per cent in pulmonary tuberculosis over 1939. Non-pulmonary tuberculosis has shown an increase of about 17 per cent over 1939, with the increase most noticeable in tuberculosis of the spine, meninges and lymph glands. The chief increase in the meningeal cases was found in the age group under 5 in both sexes and to a lesser extent in females from 15 to 25.

Of the possible causes of this increase in both pulmonary and non-pulmonary tuberculosis, the increased virulence of the tubercle bacillus, malnutrition and deficient diet, were considered of little or no importance; tubercle bacilli in milk, examination by medical boards, exertion and strain of army life, long hours in air-raid shelters and overcrowding in factories were considered of minor importance. Long hours, overwork, strain and curtailed rest, were considered to be the most important factors in producing the increase. It has already been noted that the increase was in the age groups 15 to 45 in males and 15 to 35 in females, the period of maximum working activity when long hours of overtime are frequently taken. This is supplemented by long hours of fire watching or Home-Guard duties in time normally devoted to rest or recreation. In addition to this, younger people of both sexes are patron-

izing dance halls, theatres and other places of amusement in numbers as high or higher than was the case at the outbreak of hostilities, further sacrificing hours of rest and healthful recreation. The conclusion is drawn that this combination of factors is responsible for the increase in pulmonary and non-pulmonary tuberculosis since the outbreak of war in 1939 in Glasgow.

R. J. W.

A Case of Unilateral Clubbing of the Fingers with a Summary of the Literature

R. Ewing Rodgers, M.D., M.R.C.P.

British Medical Journal Sept., 1941, p. 439

A case of syphilitic aortitis with right subclavian aneurysm and secondary unilateral clubbing of the fingers of the right hand is presented. The aneurism decreased in size with treatment, but the patient voluntarily discontinued treatment after 3 months. When seen 6 months later the aneurism was larger and the clubbing more pronounced.

Of the 29 cases of unilateral clubbing of the fingers reported in the literature, 24 occurred with aneurysms, chiefly of the subclavian arteries. Of the other five, pressure was observed on the vessels and nerves of the affected limb from an old dislocation of the shoulder, carcinoma of the right upper lobe bronchus, a bullet which passed through the axillary vascular region with no specified lesion described and 2 cases of phlebectasia. In the case reported in this paper there was, clinically, obstruction of the vessels in the affected arm as shown by oedema, venous dilation, pulse and blood pressure.

Of the various factors suggested as causing the clubbing, there have been suggested interference with axillary circulation, interference with sympathetic nerve supply to the axillary vessels and toxaemia. Two of the reported cases showed disappearance of the clubbing partially or completely after operation on the aneurism. It is suggested that local circulatory embarrassment causes anoxaemia and the clubbing.

R. J. W.

A Clinical Study Concerning the Value of Biolac

I. As a Suitable Food

II. As a Source of Available Iron for Infants

R. Cannon Eley, M.D.,
Boston, Mass.

I. This study was designed to determine the value of Biolac as a satisfactory source of food in artificially fed infants. The criteria employed in the determination were: increase in weight, increase in sitting height, increase in length, increase in head and chest circumference, development of motor and mental activity, dentition and regularity and character of the stools in a group of infants fed witl Biolac as compared with a control group of infants fed modified pasteurized milk. The study was carried on for 5 months on 50 normal infants who were divided into two groups, one receiving Grade A pasteurized milk, corn syrup and water and the other, Biolac.

Of all the above determinations, the only one of significance was that in which the stools of babies fed Biolac were softer, more easily expelled than those found with the modified milk formula. Indeed they closely simulated those seen in breast fed infants.

II. Normally there is very little evidence of iron-deficiency anaemia before the 8th to 10th week, depending on the blood level of the mother during gestation and the amount of iron stored in the foetus before birth. After this time there may be a need for iron and such may be supplied in medicinal form or in the food. The efficacy of such preparations may be determined by the reticulocyte response.

Over a period of 18 weeks, each infant was fed (1) Biolac without iron (it normally contains 7-9 mgms.), (2) Biolac with iron, (3) Biolac without iron but 1 c.c. Elixir Ferrous Sulphate given between meals, (4) Biolac without iron plus 4 c.c. of the elixir. In the first instance there was a steady fall in R.B.C. and haemoglobin estimation which in the second rose and was accompanied by a reticulocyte response amounting to 2.1%.

In the third, there was an even greater reticulocyte response as was the case in the fourth instance.

Although the iron given between meals is more efficient than when it was included in the food, the latter has a distinct advantage in being more palatable and convenient.

Thus Biolac is not only a satisfactory source of food for artificially fed infants but also contains adequate iron for that period of life when milk alone is the principal food.

G. G. C.

The Operability of Carcinoma of the Rectum

British Medical Journal, Sept. 20, 1941

This paper written by J. C. Goligher, M.B., Ch.B., F.R.C.S., takes the form of a review of 1,186 cases of carcinoma of the rectum occurring from 1930-39 in St. Mark's Hospital, London, with an eye to the operability of the disease in its various degrees and types.

Operability is defined as that state of the patient considered by the surgeon as favourable for operation, and as having a possibility of complete cure.

The conclusions drawn from this study are:

8% of cases were deemed inoperable due to the poor general condition of the patient.

32% were considered inoperable because of the inroads made by the growth, as evidenced by secondary hepatic growths, peritoneal and lymph node involvement, and fixity of the rectal mass.

The author adds a word of advice re "fixity" of the growth, stating that the fixation of a large rectal mass cannot be accurately gauged by rectal examination, and that only a laparotomy can decide definitely. In this series, the anterior type of fixation occurred most frequently, and is regarded as the most dangerous type.

It is also noted that secondaries of the liver were often to be found buried deep in the liver substance at autopsy, a few days after a laparotomy at which the liver was found to be "clear."

Again, the author reminds us that the majority of "adhesions" binding malignant rectal growths to surrounding parts are inflammatory in nature, and not neoplastic.

All in all, the operability rate for both sexes was found to be 60%-58.5% for males, and 64.5% for females, and the age group presenting the highest operability rate was found to be the 40-49 year group, since the rate was lower above and below this group.

J. G. M.

Renal Complications of Sulphapyridine Therapy

Sydney M. Laird, M.D.

From

The Lancet, Sept. 6, 1941

Much of the immediate material in this paper was gained from clinical observations on patients in a military hospital whose histories are so presented.

Renal complications, presenting a specific clinical picture, are now recognized as the resultant of intensive dosage of Sulphapyridine. The clinical picture may take one of 3 forms which represent progressive stages of the same process. In the first, microscopic haematuria is found sometimes associated with vague abdominal pain; in the second, gross haematuria with severe pain, malaise, vomiting and pyrexia; in the third, diminished output of grossly blood stained urine which may lead to anuria, nitrogen retention and death.

Such complications are invoked by the precipitation of Acetyl-Sulphapyridine crystals in the tubular system of the kidneys. These sharp crystals may form a nidus for the formation of calculi which by mechanical irritation produce the haematuria and reflex spasm of the ureter and so leads to hydronephrosis, anuria nitrogen retention and death.

To aleviate any degree of haematuria due to Sulphapyridine, the administra-

tion of the drug should be stopped and its rapid elimination instituted by forcing the fluid intake up to 3000 c.c. in 24 hours. The early recognition of these complications—by daily microscopic urine analysis is important, for in the first and second stages this simple treatment is most effective. In the third stage, a favourable prognosis depends on the immediate institutions of ureteric catheterization and lavage.

The prevention of significant haematuria during Sulphapyridine therapy in which the dosage exceeds 5 grains per day, depends essentially on a fluid intake of at least 3000 c.c. per 24 hours and an urinary output of 1500 c.c.

G. G. C.

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